BL-B01D1, a novel EGFR×HER3-targeting ADC, demonstrates robust anti-tumor efficacy in preclinical evaluation

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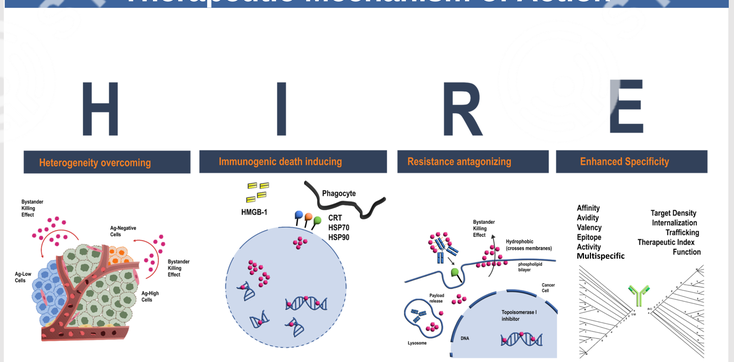
Abstract

EGFR and HER3, members of the human epidermal growth factor receptor (ErbB) family, are targeted in cancer therapy due to their over-expression and pathway dependence in common human epithelial carcinoma tumors. To develop a promising therapeutic anti-tumor agent, we generated BL-B01D1, an EGFR×HER3-targeting ADC, which can bind to EGFR and/or HER3 positive cells and is expected to be superior to anti-EGFR and anti-HER3 ADCs. It is comprised of a bispecific antibody against EGFR/HER3 (SI-B001), a cathepsin B cleavable linker, and a novel topoisomerase I inhibitor agent (Ed-04), which is a derivative of the alkaloid camptothecin, driving cell cycle arrest at the S phase and subsequent apoptosis. BL-B01D1 achieves a high drug-to-antibody-ratio (DAR=8) with a highly stable linker.

The pharmacological potential of this ADC was evaluated in comparison to its parental single antigen-targeting ADCs in xenograft models composed of either the human colorectal cancer cell line SW620 or pancreatic cancer cell line BxPC3. The tumor inhibition activity of BL-B01D1 was compared with ADCs prepared from each parental anti-EGFR or anti-HER3 mAb conjugated with the same linker and payload. The bispecific ADC, BL-B01D1 exhibited stronger tumor inhibition capacity than the anti-EGFR ADC and the anti-HER3 ADC separately.

The preclinical studies suggest BL-B01D1, as an EGFR×HER3-targeting ADC, might be a promising novel agent with activity toward a broad range of human cancers. The clinical phase I has been progressing and the available data exhibit excellent efficacy but low levels of targeted toxicity in the non-small cell lung cancer (NSCLC) treatment setting. Overall, these data suggest BL-B01D1 has potential to serve as a novel, efficacious therapeutic agent for NSCLC with similar therapeutic impact as DS-8201 has in breast cancer treatment.

Therapeutic Mechanism of Action



BL-B01D1 Cell Binding is determined by EGFR and not HER3

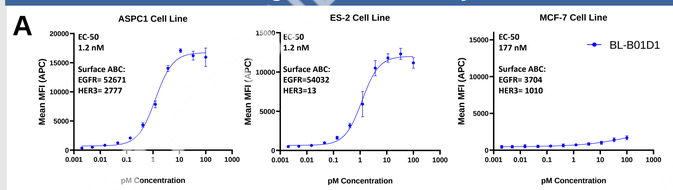
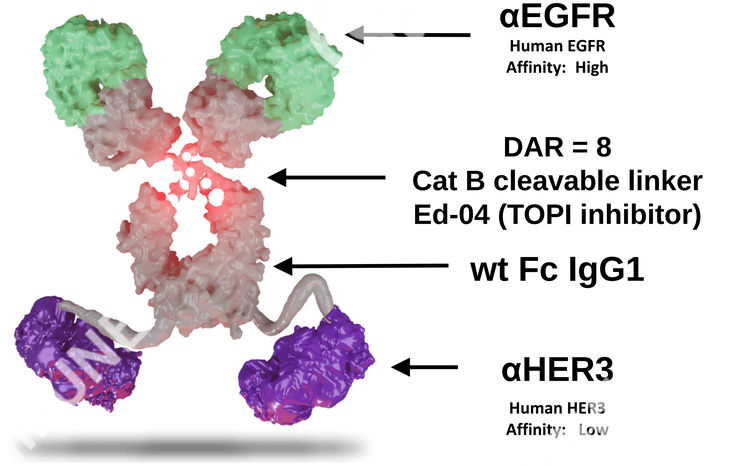
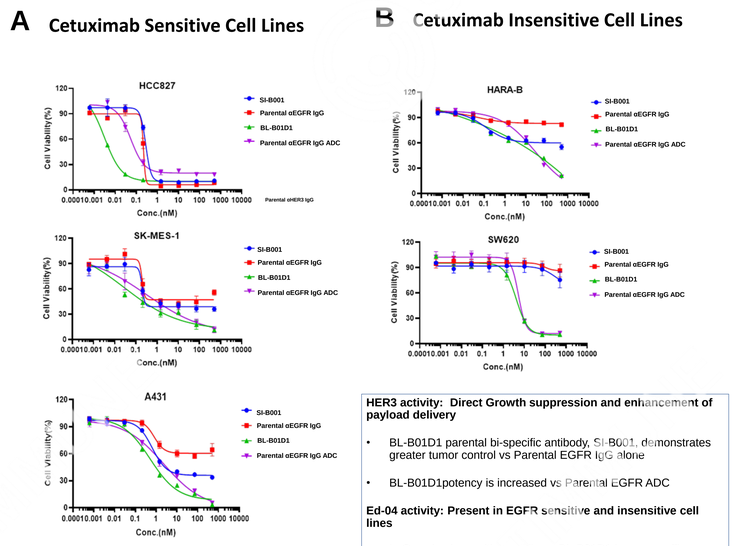


Figure 1. BL-B01D1 structure mediates specific antigen binding and multi-domain target mediated cytolytic function. ASpC-1 cells (EGFR+HER3+), ES-2 cells (EGFR+,HER3-) and MCF-7 cells (EGFRlo, HER3+) were used to test BL-B01D1 binding to cells with differential expression of target antigens. These results indicate that BL-B01D1 does not bind effectively to Cells with very low EGFR, despite expression of HER3. The antigen density of HER3 is lower than EGFR in the cell lines tested

BL-B01D1 Bi-specific ADC



BL-B01D1 proliferation inhibition is mediated by EGFR and HER3 binding and Ed-04 specific cytotoxicity *in vitro*



HER3 activity: Direct Growth suppression and enhancement of payload delivery

- BL-B01D1 parental bi-specific antibody, SI-B001, demonstrates greater tumor control vs Parental EGFR IgG alone
- BL-B01D1potency is increased vs Parental EGFR ADC

Ed-04 activity: Present in EGFR sensitive and insensitive cell lines

- In Cetuximab sensitive cell lines, BL-B01D1 improves efficacy compared to SI-B001, demonstrating Ed-04 contribution to cytotoxicity

Figure 2. BL-B01D1 specific cytotoxicity to cancer cell lines *in vitro*
Cetuximab sensitive and Cetuximab insensitive cell lines were treated with either SI-B001 the parental bi-specific of BL-B01D1, the anti-EGFR mAb Cetuximab, BL-B01D1 or the ADC composed of Cetuximab and Ex0115.

BL-B01D1 shows superior control of Xenograft Tumor growth *in vivo*

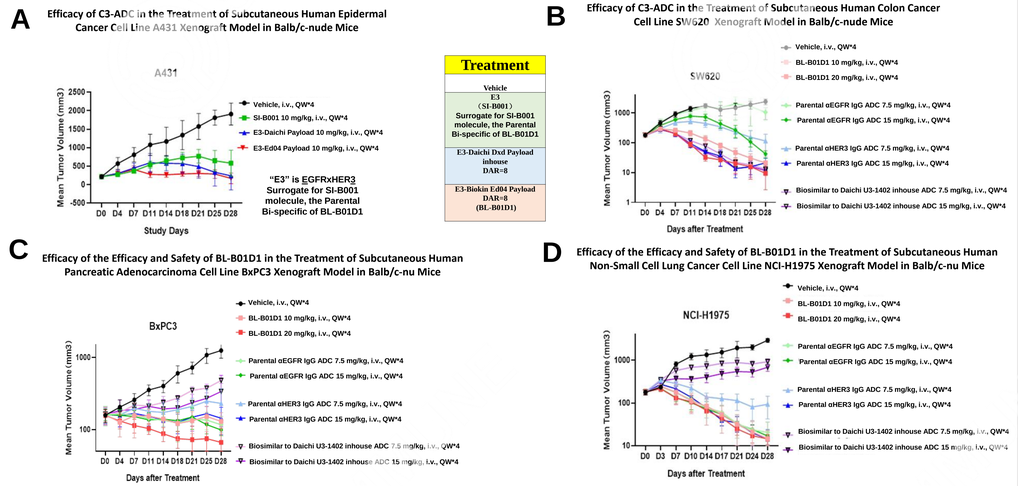
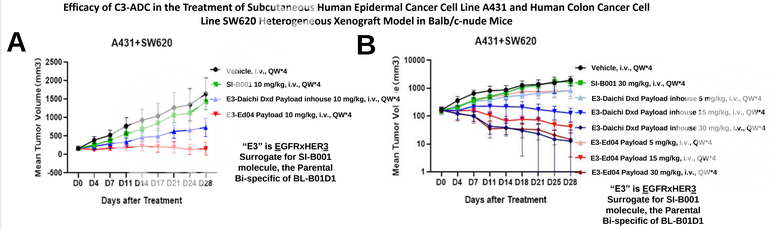


Figure 3. BL-B01D1 comparative testing in tumor xenograft models. Payload comparison (A). Bi-specific parental component comparison and comparator evaluation (B-D)

Heterogenous EGFR Xenograft Tumor Control by BL-B01D1 *in vivo*



- BL-B01D1 payload shows superior bystander effect in treatment of heterogenous tumor compared to Daichi payload
- Between 5 and 30 mg/mL BioKin payload is superior to Daichi payload in a model of heterogenous tumor
- Suggesting a treatment window for BL-B01D1 with greater opportunity to prevent tumor relapse

Figure 4. BL-B01D1 comparative testing in EGFR heterogenous tumor xenograft models. Payload comparison (A,B)

Summary

- BL-B01D1, an EGFR×HER3-targeting ADC, which can bind to EGFR and/or HER3 positive cells
- BL-B01D1 is comprised of a bispecific antibody against EGFR/HER3 (SI-B001), a cathepsin B cleavable linker, and a novel topoisomerase I inhibitor agent (Ed-04) with a drug-to-antibody-ratio of 8 (DAR=8)
- Ed-04 is a derivative of the alkaloid camptothecin, driving cell cycle arrest at the S phase and subsequent apoptosis showing superior bystander activity compared to Daichi payload (in house)
- BL-B01D1 exhibited stronger tumor inhibition capacity than the parental anti-EGFR ADC and the anti-HER3 ADC in colorectal cancer SW620 and pancreatic cancer BxPC3 xenograft models
- As an EGFR×HER3-targeting ADC, BL-B01D1 might be a promising, novel agent, with activity toward a broad range of human cancers

Acknowledgments

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References

BL-B01D1 clinical trials:

Title	URL
A Clinical Study of BL-B01D1 in Patients With Multiple Solid Tumors Such as Recurrent or Metastatic Gynecological Malignancies	https://ClinicalTrials.gov/show/NCT05803018
A Clinical Study of BL-B01D1 in Patients With Multiple Solid Tumors Such as Locally Advanced or Metastatic Urinary System Tumors	https://ClinicalTrials.gov/show/NCT05785039
A Study of BL-B01D1 in Patients With Locally Advanced or Metastatic Gastrointestinal Tumor and Other Solid Tumor	https://ClinicalTrials.gov/show/NCT05262491
A Study of BL-B01D1 in Patients With Locally Advanced or Metastatic Solid Tumor	https://ClinicalTrials.gov/show/NCT05194982
A Study of BL-B01D1 in Patients With Locally Advanced or Metastatic Urological Tumors and Other Solid Tumors	https://ClinicalTrials.gov/show/NCT05393427
A Study of BL-B01D1 in Patients With Unresectable Locally Advanced or Metastatic Breast Cancer and Other Solid Tumors	https://ClinicalTrials.gov/show/NCT05470348